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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/011,910	02/17/98	ABRIGNANI S	0336.001

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EXAMINER	
BRUMBACK, B	
ART UNIT	**PAPER NUMBER**
1643	6

DATE MAILED: 09/14/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/011,920	Applicant(s) Abrignani
	Examiner Brenda Brumback	Group Art Unit 1643

☒ Responsive to communication(s) filed on *Jul 27, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) *16 and 18-20* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-15 and 17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4* .

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I, claims 1-15 and 17 in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

2. The information disclosure statement filed 07/27/99 has been received and made of record as Paper # 4; however, it fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein as reference C3 has not been considered. All other listed publications were considered. A signed copy is attached hereto.

Specification

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

4. Claims 1-15 and 17 are objected to because they lack proper introduction. The present Office practice is to insist that each claim be the object of a sentence starting with a phrase such as "I (or we) claim" or "What is claimed is" or "That which is claimed is". See MPEP 608.01 (m). Appropriate correction is required.

5. Claims 7 and 10 are missing the " ." at the end of the sentence.

Claim Rejections - 35 USC § 112/101

6. Claims 1-15 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 11-15, and 17 recite a protein capable of specifically binding a protein of hepatitis C virus (HCV) or a "functionally equivalent variant or fragment thereof". It is unclear whether the phrase "functionally equivalent variant or fragment thereof" is intended to modify the protein which binds an HCV protein or the HCV protein itself. Additionally, the specification fails to teach the metes and bounds of a "functionally equivalent variant". It is unclear what function is to be considered in determining equivalency. It is also unclear how proteins can vary and still retain functional equivalency. Finally, the specification fails to teach the metes and bounds of "fragment". Is fragment intended to encompass peptides of any length? If so, are

fragments of as little as a single amino acid intended to be encompassed within the instant claims? If not, how many (and which) amino acids that make up the native protein are encompassed within the definition of "fragment"?

Claim 2 recites a protein which is "functionally unglycosylated". Is the "functionally" unglycosylated intended to have the same meaning as "functionally equivalent"? Recitation of "functionally" twice in the instant claim renders the claim indefinite.

Claim 4 is drawn to a process for the preparation of a protein comprising the step of culturing cells exhibiting binding to an HCV protein and purifying from a cell preparation a protein. It is unclear whether the "cell preparation" recited is intended to be the same or a different population from that of the cultured cells. Thus, the claim is indefinite.

Claims 5 and 10 recite a "plasma cell membrane". It is unclear whether this phrase is intended to describe a membrane of a plasma cell or if it is intended to describe a plasma membrane of a cell. If the intended recitation is that of a cell membrane, it is suggested that the term "plasma" be deleted.

Claims 6 and 10 are indefinite for recitation of "hyperexpression" of a protein. The metes and bounds of "hyperexpression" are not defined in the specification. The standard of expression used for measuring and defining "hyperexpression" is not described. Therefore, the claim is indefinite.

Claim 7 recites a process but fails to set forth any active steps involved in the method/process because "subjected to" does not describe an active step; therefore, it is unclear

what method/process applicant is intending to encompass. Similarly, claims 8 and 9 recite "involves", which is not an active step. A claim is indefinite wherein it recites a process without delineating active steps involved in that process.

Claim 7 recites 33 and 50% but does not describe what the percentages are a portion of. Thus the claim is indefinite.

Claim 8 is indefinite for the recitation of "at least one step of hydrophobic interaction chromatography". It is unclear what step of hydrophobic interaction chromatography is intended to be incorporated into the claimed process. The instant specification fails to teach the steps of hydrophobic interaction chromatography. It is also unclear whether " hydrophobic interaction chromatography" is intended to encompass a single step which is to be practiced once or more during the claimed process or if "hydrophobic interaction chromatography" encompasses plural steps, one of which is to be incorporated somewhere into the claimed process.

Claim 9 recites "one step of acetone precipitation". The specification fails to teach the steps of acetone precipitation encompassed within the claim. If acetone precipitation is intended to be a single step, it is unclear where this step fits into the claimed process. Thus, the claim is indefinite.

The preamble of claim 10 is confusing for recitation of "wherein comprising"(line 1), which results in improper syntax. Correction is required.

Claim 10 recites in step i), "preparing a ... preparation...". This step fails to describe an active step in the claimed process. In step iv) the term "resuspending" is used. Unless the

intention of the described step is to suspend the precipitate back into the original cell preparation, the term "suspending" should be substituted for "resuspending". Finally, "subjecting to" in step iv) does not describe an active method step. Correction is required.

Claim 11 recites a "method for treating an infection of HCV". This phrase renders the claim indefinite as it connotes that the virus itself is infected with some agent, rather than the virus being the infecting agent in a patient. Correction is required.

Claim 12 recites "optionally as a pharmaceutically acceptable salt" but does not list the salt. It is suggested that if the specific salt is not intended to be a limitation of the claim, that the term "as" be deleted. Additionally, claim 21 is indefinite because it is unclear what is intended by the term "optionally". If an ingredient, a step, or other structural element is truly optional, i.e. its presence is not necessary for attainment of the result that is the object of the invention, the recitation thereof does not belong in the claim.

Claim 13 is indefinite for the recitation of "brought into association with" because the metes and bounds of such an "association" cannot be determined.

Claim 15 provides for the use of a protein according to any one of claims 1-3, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

7. Claim 15 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

8. Claims 1-15 and 17 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As described *supra*, claims 1-4, 11-15, and 17 recite a protein capable of specifically binding a protein of hepatitis C virus (HCV) or a "functionally equivalent variant or fragment thereof". Because the metes and bounds of "functionally equivalent" and "fragment" are unclear, the skilled artisan would be unable to make the invention as claimed. Similarly, because the meaning of "functionally unglycosylated" as it is applied to claim 2 is also unclear, the skilled artisan would be unable to make the invention as claimed.

As described *supra*, the definition, order, and frequency of the steps of ammonium sulfate precipitation, hydrophobic interaction chromatography, and acetone precipitation recited in claims 7, 8, and 9 are indefinite; thus, the skilled artisan would be unable to practice the claimed

process. Similarly, the skilled artisan would be unable to practice the process of claim 10 due to the indefiniteness of the recited steps.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among these factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention and the breadth of the claims: Claims 11-15 are drawn to pharmaceutical compositions and methods of treating HCV infection in a patient comprising administering to the patient the 24kD protein of claim 1, 2, or 3, which is capable of binding a protein of HCV. As is claimed, the 24kD protein of claims 1, 2, and 3 encompasses antibodies which bind to HCV or any HCV protein, as well as a putative cellular receptor for HCV.

The state of the prior art and the predictability or lack thereof: Rice (Hepatology; 29,3:990-992, 1999) teaches that the mechanisms of HCV cell entry are unknown; however, it is known that HCV envelope protein E2 binds human CD81, a 24kD protein expressed on various cell types, including B lymphocytes and hepatocytes (see the abstract). Rice teaches that although the binding of HCV E2 to CD81 offers clues as to how HCV attaches to cells, it does not prove that CD81 is the cellular receptor for HCV. Rice also teaches that the CD81 protein does not necessarily have any therapeutic application *in vivo* and teaches that any potential therapeutic application "will depend on many unknowns". Rice teaches that it is presently unknown whether the E2-CD81 interaction is essential for HCV infection or whether other cell surface molecules also allow attachment and entry of infectious HCV (see page 990, column 2, first full paragraph and the paragraph bridging pages 990 and 991). Thus, the art teaches that the CD81 protein may or may not have therapeutic application in the future. The art does not teach how pharmaceutical compositions useful for treating HCV infection comprising the CD81 protein can be made or how they can be administered in order to achieve therapeutic levels *in vivo* and block viral entry and infection. Furthermore, although Rice teaches that antibodies capable of blocking HCV E2

binding might also neutralize HCV infectivity *in vivo*, the art does not teach how pharmaceutical compositions comprising neutralizing antibodies could be made, what neutralizing antibodies would be effective *in vivo*, or how these antibodies could be administered so as to achieve therapeutic levels *in vivo* for effective treatment of HCV infection in a patient (see page 900, *Comments*, the paragraph bridging columns 1 and 2).

The amount of direction or guidance present and the working examples: Because the art does not teach that proteins which bind to HCV have any current therapeutic application for treatment of HCV infection *in vivo*, the instant disclosure must contain sufficient detail to enable the skilled artisan to formulate pharmaceutical compositions comprising such proteins and to use these formulations for treating HCV infection in a patient. There are no such teachings found in the instant specification. The teachings in the specification are limited to elucidation of a 24kD cellular protein which binds to HCV and purification of the protein from cell preparations *in vitro*. There are no working examples describing blocking of HCV attachment to susceptible cells by administering the claimed protein either *in vitro* or *in vivo*. There are no working examples describing preparation of pharmaceutical compositions or administration of such compositions *in vivo*. There are no working examples describing treating HCV infection *in vivo*.

The quantity of experimentation needed: For the reasons described *supra*, the skilled artisan would be unable to make or use the claimed invention, absent extensive and undue experimentation.

Claim Rejections - 35 USC § 102/103

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. Claims 1 and 17 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rosa et al. (Proc. Natl. Acad. Sci., 93:1799-1763, March 1996; of record as reference C.7 in Paper # 4).

The claimed invention is drawn to a 24kD protein which specifically binds to HCV or to any size fragment of the 24kD protein or to any other protein which is the functional equivalent of the 24kD protein; therefore, it encompasses any and all proteins which specifically bind to HCV, including HCV-specific antibodies, and to diagnostic kits comprising the proteins.

Rosa et al. teach polyclonal antibodies which bind to the HCV glycoprotein E2 and teach that the antibodies can be used as diagnostic reagents for blocking the binding of HCV to susceptible cells (see the entire document).

b. Claims 1 and 17 are also rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Mehta et al. (WO 93/04205; of record as reference B.3 in Paper # 4). Mehta et al. teach monoclonal antibodies which specifically bind HCV E2/NS1 antigen and teach diagnostic assay kits comprising the antibodies (see the entire document).

c. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minutello et al., (Journal of Hepatology, 17 [Suppl.1]:55-56, 1992) in view of Rowlands et al., pp. 795-808 in Henry, J.B. *ed.*, Clinical Diagnosis and Management by Laboratory Methods, 18th ed., W.B. Saunders Company, Philadelphia, 1991).

The claimed invention is drawn to a protein having a molecular weight of about 24kD which is capable of specifically binding HCV and to functional equivalents and fragments thereof. Dependent claims 2 and 3 recite the protein as a functionally unglycosylated transmembrane protein.

Minutello teaches that HCV antigens stimulate proliferation of T and B lymphocytes specific for HCV proteins *in vivo* (see the entire document). Rowlands teaches that T cells have

antigen recognition sites specific for the stimulating antigen and that B cells present cell surface immunoglobulins which are specific for the stimulating antigen (see page 797, column 2, second full and last partial paragraphs). Rowlands teaches that T and B cells have a number of surface proteins of varying molecular weights (MW), including proteins of approximately 24kD (see page 797, Table 31-2, CD3 for example). Thus, the T cell which specifically binds HCV comprises the claimed protein, or in the alternative, is a functional equivalent of the HCV-specific binding protein. The HCV-specific immunoglobulin antibody found on the surface of the B-cell anticipates the claimed protein or, in the alternative, is a functional equivalent thereof.

d. Claims 4-8, 10, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minutello et al. in view of Rowlands et al., as applied to claims 1-3 above, and further in view of Shimonaka et al. (The Journal of Biological Chemistry; 269, 19:14284-14289, May 1994).

As described *supra*, Minutello teaches that T cells and B cell antibodies which are specific for HCV antigens bind HCV proteins *in vivo*. Rowlands teaches that T and B cells comprise surface proteins of varying MW, including proteins approximating 24kD. Neither Minutello nor Rowlands teaches a process for purifying the proteins from a cellular preparation, as in the claimed invention. Shimonaka et al. describe procedures for purification of cellular proteins, which include ammonium sulfate precipitation and hydrophobic interaction chromatography. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention

was made to have applied the procedures described by Shimonaka et al. for purifying the surface proteins described by Minutello in view of Rowlands. One of ordinary skill in the art at the time the invention was made would have been motivated to do so in order to obtain a preparation of suitable purity and specificity for use as a diagnostic reagent.

e. Claims 4-10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minutello et al. in view of Rowlands et al., as applied to claims 1-3 above, and further in view of Maat et al. (EPA 0 565 172).

As already described, Minutello teaches that HCV-specific T cells and HCV-specific B-cell immunoglobulins bind HCV proteins *in vivo*. Rowlands teaches that T and B cells comprise surface proteins of varying MW. Neither Minutello nor Rowlands teaches a process for purifying the proteins, as in the claimed invention. Maat et al. teach that conventional precipitation and chromatographic methods used for purification of polypeptides from cells include acetone precipitation, ammonium sulfate precipitation, and hydrophobic interaction chromatography (see page 12, lines 19-24 and 54-57). One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have applied the precipitation and chromatographic methods taught by Maat et al. to purify the surface proteins described by Minutello in view of Rowlands in order to obtain a suitable diagnostic reagent.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Chris Eisenschenk whose telephone number is (703) 308-0452. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1643 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1643 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
September 9, 1999

DONNA WORTMAN
PRIMARY EXAMINER